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NEBOKITUG TARGETS MACROPHAGE-MEDIATED MECHANISMS IN PRIMARY SCLEROSING CHOLANGITIS WITH POTENTIAL IMPACT ON DISEASE PROGRESSION

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1. Chemomab therapeutics

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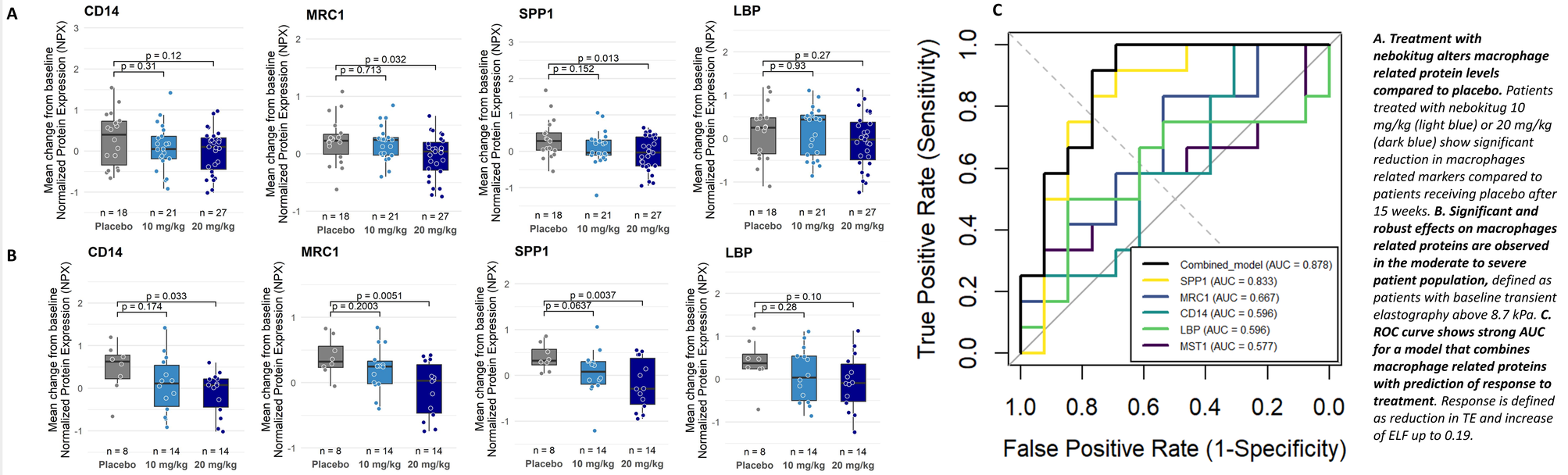
INTRODUCTION & AIM

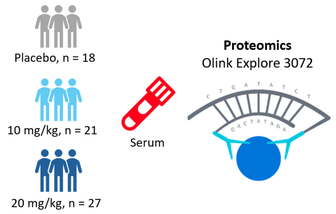
Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive inflammatory and fibrotic injury to the biliary tree. A key element of PSC pathogenesis is sustained innate immune activation, prominently involving hepatic macrophages. Elevated levels of macrophage-associated proteins-including soluble CD14, Mannose receptor C-type 1 (MRC1), and osteopontin (SPP1) observed in patients with PSC and correlate with poor clinical outcomes. Macrophage stimulating 1 (MST1), a driver of anti-inflammatory macrophage polarization, is functionally impaired by a genetic variant that is linked to PSC (our MST-1 data presented on Publication Number: 4401). Nebokitug, a monoclonal antibody against CCL24, has shown promising modulation of inflammation and fibrosis markers in the Phase 2 SPRING trial (NCT04595825) as well as modulation of macrophages activity in pre-clinical studies. Here, we evaluated its effect on macrophage-driven activity in patients with PSC by assessing changes in key macrophage related biomarkers that are known to be clinically meaningful through their association with clinical outcomes.



A. Treatment with nebokitug alters macrophage related protein levels compared to placebo. *Patients treated with nebokitug 10 mg/kg (light blue) or 20 mg/kg (dark blue) show significant reduction in macrophages related markers compared to patients receiving placebo after 15 weeks.* ***B. Significant and robust effects on macrophages related proteins are observed in the moderate to severe patient population,*** *defined as patients with baseline transient elastography above 8.7 kPa.* ***C. ROC curve shows strong AUC for a model that combines macrophage related proteins with prediction of response to treatment****. Response is defined as reduction in TE and increase of ELF up to 0.19.*

METHODS

The SPRING study is a randomized, double-blind, placebo controlled trial in patients with PSC receiving nebokitug 10 or 20 mg/kg IV every 3 weeks for 15 weeks or placebo. Levels of sCD14, MRC1, LBP, SPP1 were assessed by Olink® proximity extension assay (PEA) on serum samples available from 66 patients (placebo n=18; nebokitug 10 mg/kg n=21 and 20 mg/kg n=27) at baseline and week 15. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of these biomarkers to predict treatment response as measured by changes in ELF score and liver stiffness measurement (LSM)



RESULTS

Nebokitug treatment led to dose-dependent reductions in serum macrophage-related proteins as compared to placebo treated patients, predominantly in patients with moderate/advanced disease (LSM>8.7 Kpa at baseline), including soluble CD14 (20 mg/kg p=0.03; 10 mg/kg p=0.17) MRC1 (20 mg/kg p=0.005; 10 mg/kg p=0.2) and SPP1 (p=0.003; 10 mg/kg p=0.06).

Macrophage activity is known to play a key role in PSC pathophysiology and its modulation may impact disease progression. Accordingly, changes seen in these biomarkers following treatment with nebokitug were associated with improvements seen in ELF score and LSM (AUC=0.87).

CONCLUSIONS

Nebokitug modulates key macrophage-related biomarkers in patients with PSC that have been shown to correlate with disease progression. These data suggest a potential role for nebokitug in modifying disease progression and support continued clinical evaluation.

ACKNOWLEDGEMENTS

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